

# Family History of Breast Cancer as a Risk Factor for Ovarian Cancer in a Prospective Study

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**BACKGROUND.** A family history of breast cancer has been associated with increased ovarian cancer risk. However, few studies have assessed risk according to characteristics that suggest an inherited cancer susceptibility disorder, such as earlier-than-usual age at cancer diagnosis, family members with double primary cancers of different types, multiple relatives with cancer, and cancer in both members of paired organs.

**METHODS.** Ovarian cancer risk was assessed according to a detailed breast cancer family history among 49,975 participants in the Breast Cancer Detection Demonstration Project Breast Cancer Defection Demonstration Project (BCDDP) Follow-up Study (1979–1998). In all, 362 incident ovarian cancers were identified during follow-up and rate ratios (RRs) were calculated by Poisson regression.

**RESULTS.** Breast cancer in a first- or second-degree relative was associated with increased risk of ovarian cancer (RR = 1.4; 95% confidence interval [CI] = 1.1–1.7). Having 2 or more affected first-degree relatives was associated with increased risk (RR = 1.8; 95% CI = 1.1–2.8), especially for women diagnosed with ovarian cancer before age 60 (RR = 4.2; 95% CI = 1.9–9.2) or with a personal history of breast cancer (RR = 3.7; 95% CI 1.8–7.7). Risk was also particularly high for women with 2 or more first-degree relatives with breast cancer and at least 1 affected relative diagnosed before age 50 (RR = 2.6; 95% CI = 1.4–4.8) or with bilateral breast cancer (RR = 4.2; 95% CI = 1.7–10).

**CONCLUSIONS.** A detailed breast cancer family history as well as an individual's age and personal history of breast cancer are useful for identifying women at elevated genetic risk of ovarian cancer. *Cancer* 2006;107:1075–83. Published 2006 by the American Cancer Society.\*

**KEYWORDS:** breast cancer, family history, ovarian cancer.

Ovarian and breast cancers share selected reproductive, hormonal, and genetic risk factors. For example, breast and ovarian cancers occur more often than expected as independent double primary malignancies in the same women, which may reflect both genetic and environmental factors.<sup>1</sup> The hereditary breast-ovarian cancer syndrome, largely attributable to mutations in the *BRCA1*

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and BRCA2 genes, is thought to account for most hereditary ovarian cancers.<sup>2</sup>

A first-degree family history of breast cancer has been associated with increased risk of ovarian cancer in most,<sup>3-11</sup> but not all,<sup>12,13</sup> relevant epidemiologic studies. However, detailed epidemiologic data on risk according to clinical features that typically reflect hereditary cancer syndromes, such as earlier-than-usual age at cancer diagnosis, family members with double primary cancers of different types, multiple relatives in multiple generations with cancer, and cancer in both members of paired organs ("bilateral-ity"),<sup>14</sup> are limited and inconsistent.<sup>3,4,6,7,12,13</sup>

Accurately assessing detailed aspects of a family history of breast cancer can be pertinent to genetic testing, screening, and prevention interventions for ovarian cancer.<sup>15</sup> In particular, with the advent of clinical testing for mutations in the *BRCA1* and *BRCA2* breast/ovarian cancer susceptibility genes, identifying individual patients who might benefit from formal cancer genetic risk assessment is a challenge.<sup>16</sup> To further characterize the risk of ovarian cancer associated with characteristics of a family history of breast cancer that might reflect hereditary cancer syndromes, we analyzed data from a cohort study of largely postmenopausal women.

## **MATERIALS AND METHODS**

The women in this study were former participants in the Breast Cancer Detection Demonstration Project (BCDDP), a breast cancer screening program conducted between 1973 and 1980. The BCDDP provided up to 5 annual breast examinations to 283,222 women at 29 screening centers in 27 cities throughout the US.

The National Cancer Institute (NCI) initiated a separate follow-up study in 1979, as the screening study neared completion. It included: 1) all women diagnosed with breast cancer during the BCDDP ( $n = 4,275$ ); 2) all women who had undergone benign breast surgery ( $n = 25,114$ ); 3) all women recommended for a surgical consultation, without subsequent biopsy having been performed ( $n = 9,628$ ); and 4) a sample of women neither recommended for surgical consultation nor undergoing a biopsy ( $n = 25,165$ ). The follow-up study was conducted in 4 phases. The first phase (1979-1986), involved the administration of a baseline and up to 6 annual telephone interviews. Phases II (1987-1989), III (1993-1995), and IV (1995-1998) data collections were conducted through self-administered questionnaires mailed to all participants not known to be dead. Nonrespondents to the mailed questionnaires were interviewed by telephone, when possible. In-

stitutional Review Board approval was obtained for this study and all participants provided informed consent.

## **Ascertainment of Data on Family History of Breast Cancer and Potential Confounders**

Information on breast cancer in the mother, sisters, daughters, grandmothers, and aunts of study subjects was obtained at the baseline interview and was updated on each Phase I annual interview. The number of each type of relative with breast cancer was also obtained. Supplemental information on the number of aunts, full- and half-sisters, and daughters; how many had ever had breast cancer; age at their diagnosis; and whether breast cancer was unilateral or bilateral was obtained on the Phase II questionnaire. With the exception of numbers of aunts, sisters, and daughters, this information was updated on the Phase III and Phase IV questionnaires. Information on a family history of ovarian cancer in a first-degree relative, i.e., mother, sister(s), or daughter(s), was ascertained only on the Phase IV questionnaire. Information on other potential confounding factors, including menopausal status, duration of oral contraceptive use and menopausal estrogen therapy, personal history of breast cancer, and parity was also obtained on the baseline questionnaire. Information on parity and oral contraceptive use was ascertained only at baseline and during Phase I, respectively, but information on the other risk factors was updated at each phase of the study.

## **Endpoint Ascertainment**

Participants' lifetime history of ovarian cancer was collected on the Phase II questionnaire and updated in Phases III and IV. Pathology reports were sought for all self-reported cancers. The cohort was linked to the National Death Index (NDI), with cause of death coded from death certificates. In all, 72% of the women who completed a baseline interview and 85% of the women who completed a Phase II questionnaire were also linked to 19 state cancer registries.

## **Analytic Cohort**

### **Study population**

Of the 64,182 eligible women enrolled in the BCDDP Follow-up Study, 61,430 (95.7%) completed the baseline interview. Women with bilateral oophorectomy ( $n = 11,358$ ) or ovarian cancer ( $n = 93$ ) before the baseline interview, as well as 5 women whose date of death could not be confirmed, were excluded from the analysis. Of the 49,975 women eligible for inclusion, 42,068 (84%) completed the Phase II questionnaire. Of 43,789 women eligible for the Phase III

questionnaire, 36,624 (84%) completed it, and of 40,059 eligible for the Phase IV questionnaire, 34,826 (87%) completed it. Missing Phase II questionnaires were due to death (5.0%), illness (0.8%), refusal (3.6%), and inability to contact the study participant before the end of the phase (6.6%). The corresponding percentages for missing Phase III and IV questionnaires were 1.0%, 1.0%, 3.0%, and 11.0%; and 6.0%, 2.0%, 1.0%, and 4.0%, respectively.

### Analytic Dataset

#### Case definition

Incident ovarian cancers (ICD-O codes 183.0, 183.3–183.9, and ICD-9 codes 183.0, 183.3–183.9, and 236.2)<sup>17</sup> were identified through self-report on the follow-up questionnaires, pathology reports, and linkage to the NDI and state cancer registries. Borderline tumors were excluded.

Of the 362 cases identified, 173 were identified by self-report on the follow-up questionnaires; 88% of these were confirmed by pathology reports ( $n = 141$ ), state cancer registries ( $n = 10$ ), or subsequent death certificates ( $n = 2$ ); 20 self-reported cases were unconfirmed, but were included in the analyses because of the 88% confirmation rate for self-reported cases. Five cases were identified by pathology reports retrieved for other self-reported conditions, 79 by state cancer registries, and 105 by the NDI, from which we retrieved available information from death certificates, including date of diagnosis. If date of diagnosis was not available from the death certificate, we used date of death as date of diagnosis.

#### Statistical analysis

Follow-up began at the date of the baseline interview. Women contributed person-time until the earliest of the following dates: ovarian cancer diagnosis, bilateral (or second) oophorectomy, death, completion of the Phase IV questionnaire, or the end-of-study date. Because of linkage to the NDI and the state cancer registries, we assumed that cancer-free women not known to be dead who did not complete the Phase IV questionnaire were alive and cancer-free. We assigned their end-of-study date as the date on which they would have completed the Phase IV questionnaire, based on the average interval between questionnaires from all women who completed them.

Breast cancer in a full sister, mother, or daughter was considered a first-degree family history; breast cancer in a half-sister, grandmother, or aunt (both maternal and paternal) was considered a second-degree family history. Women were classified as having developed a particular family history (first-degree, second-degree, or unknown) at the age at the

midpoint between their first report of a positive family history and the prior interview. Women who reported a positive family history on the baseline interview were classified as having developed that family history at baseline.

Rate ratios (RRs) and 95% confidence intervals (CIs) were estimated by Poisson regression using the Epicure statistical package.<sup>18</sup> Time-dependent variables in the analyses included attained age, menopausal status, personal breast cancer diagnosis, duration of oral contraceptive use, duration of menopausal estrogen therapy, and all the breast cancer family history variables.

The RRs were adjusted for attained age and personal history of breast cancer because these were the only identified risk factors for which person-years associated with family history varied. We adjusted for family size (e.g., number of first- and second-degree female relatives) due to its influence on the extent to which a woman could develop a positive family history. Analyses for second-degree family history categories included adjustments for a first-degree family history. The reference category for all the analyses comprised women who did not have relatives with breast cancer in that category.<sup>19,20</sup> Women with no sisters were excluded from analyses of risk associated with having a sister with breast cancer, women with no daughters were excluded from analyses of risk associated with having a daughter with breast cancer, and women with no aunts were excluded from analyses of risk associated with having an aunt with breast cancer.

## RESULTS

The mean duration of follow-up for study participants was 14.3 years (median, 15.9 years; range, 0.1–19.8 years). During follow-up, 49,975 women accumulated 715,914 person-years of observation. The average age at baseline was 55 years (range, 31–89 years). Most women in the study were White (87%), with small numbers of Black (5%), Asian-American (5%), and Hispanic (2%) participants.

Fifty-four percent of person-years were associated with no breast cancer family history of any type. Eighteen percent of person-years were accrued by women with a family history of breast cancer in a first-degree relative, and 17% by women with a family history of breast cancer in a second-degree relative only; 31% were accrued by women with any family history of breast cancer (i.e., first-degree, second-degree, or both). Fifteen percent of person-years were associated with an unknown family history.

**TABLE 1**  
Percentage of Person-Years Associated With a First-Degree Family History of Breast Cancer According to Selected Factors

Risk Factor	Negative 1 <sup>st</sup> -degree family history of breast cancer (%)	Positive 1 <sup>st</sup> -degree family history of breast cancer (%)	Unsure 1 <sup>st</sup> -degree family history of breast cancer (%)	Total person-years
Attained age (y)				
<50	85.3	13.7	1.0	63,176
50-54	83.1	15.3	1.6	98,312
55-59	81.5	16.6	1.9	138,368
60-64	80.1	17.9	2.1	140,050
65-69	78.6	19.2	2.2	114,298
70-74	77.1	20.6	2.3	78,548
75+	75.1	22.4	2.5	83,161
Menopausal status				
Premenopausal	80.6	17.5	1.9	249,232
Menopausal	79.8	18.2	2.0	450,580
Unknown	80.0	17.2	2.8	16,102
Personal history of breast cancer				
No	81.1	17.0	1.9	647,592
Yes	70.9	26.7	2.4	68,321
Parity				
0	80.0	18.0	2.0	98,392
1	80.1	17.8	2.1	85,240
2	80.2	17.9	1.9	208,699
≥3	80.1	18.0	1.9	323,582
Duration of oral contraceptive use (y)				
No use	79.8	18.2	2.0	503,132
<3	80.7	17.5	1.8	105,796
3 to <9	80.6	17.6	1.8	69,198
≥9	81.8	16.2	2.0	32,203
Unknown	81.9	14.5	3.6	5585
Duration of estrogen only use (y)				
No use	80.5	17.8	1.7	344,158
<8	80.9	17.3	1.8	136,839
8 to <16	78.7	19.1	2.2	33,475
≥16	78.8	19.2	2.0	19,087
Unknown	78.9	18.9	2.2	30,901

The risk of ovarian cancer was associated positively with attained age, menopausal status, duration of menopausal estrogen therapy, family history of ovarian cancer, and personal history of breast cancer, and was associated inversely with oral contraceptive use and parity (data not shown).

Table 1 summarizes the distribution of person-time for positive and negative first-degree family history, according to selected risk factors for ovarian cancer. A greater percentage of person-years associated with a first-degree family history was evident for older attained age and a personal history of breast cancer. Person-years associated with a first-degree family history did not differ materially across categories of the other factors shown in the table.

RRs of ovarian cancer associated with different categories of breast cancer family history are shown in Table 2. Statistically significant increased RRs of ovarian cancer were observed among women with

any family history of breast cancer (RR = 1.4; 95% CI: 1.1-1.7), 2 or more first-degree relatives with breast cancer (RR = 1.8; 95% CI: 1.1-2.8), 2 or more daughters with breast cancer (RR = 4.6; 95% CI: 1.1-19), and any affected second-degree relative (RR = 1.4; 95% CI: 1.1-1.8). The RR associated with any first-degree history of breast cancer was not significantly elevated (RR = 1.1; 95% CI: 0.9-1.5). The CIs for any affected first-degree relative and any affected second-degree relative overlap, indicating no statistically significant difference in these findings. A trend of increasing risk with increasing number of affected sisters was evident, although the results were not statistically significant. There was no trend of increasing risk with increasing number of affected second-degree relatives. The RR for women with both a first- and a second-degree relative with breast cancer was elevated, but not significantly (RR = 1.3; 95% CI: 0.8-2.1).

**TABLE 2**  
**Rate Ratios (RRs) of Ovarian Cancer Associated With Family History of Breast Cancer**

Family history status	No. of person-years	No. of cases	Rate per 100,000	Adjusted* RR (95% CI)
Any family history				
No history	385,566	177	45.9	1.0 (reference)
Any affected	220,520	130	60.0	1.4 (1.1–1.7)
1 affected	155,669	90	57.8	1.3 (1.0–1.7)
2 or more affected	64,851	40	61.7	1.4 (1.0–2.0)
Unknown	109,828	55	50.1	1.1 (0.8–1.5)
Any 1 <sup>st</sup> -degree relative				
No history	573,387	279	48.7	1.0 (reference)
Any affected	128,441	74	57.6	1.1 (0.9–1.5)
1 affected	109,251	55	50.3	1.0 (0.8–1.4)
2 or more affected	19,190	19	99.0	1.8 (1.1–2.8)
Unknown	14,086	9	63.9	1.2 (0.6–2.3)
Mother				
No history	633,392	314	49.6	1.0 (reference)
Mother affected	69,519	39	56.1	1.2 (0.8–1.6)
Unknown	13,003	9	69.2	1.3 (0.7–2.5)
Sister				
No history	454,730	228	50.1	1.0 (reference)
Any affected	62,739	41	65.3	1.2 (0.8–1.7)
1 affected	53,611	33	61.5	1.1 (0.8–1.6)
2 or more affected	9,128	8	87.6	1.5 (0.7–3.1)
Unknown	6946	6	86.4	1.5 (0.6–3.3)
Daughter				
No history	515,547	252	48.9	1.0 (reference)
Any affected	5,664	6	105.9	1.7 (0.7–3.9)
1 affected	4964	4	80.6	1.3 (0.5–3.6)
2 or more affected	700	2	285.7	4.6 (1.1–19)
Unknown	5486	5	91.1	1.7 (0.7–4.2)
Any 2 <sup>nd</sup> -degree relative				
No history	455,025	214	47.0	1.0 (reference)
Any affected	125,317	74	59.0	1.4 (1.1–1.8)
1 affected	96,212	61	63.4	1.5 (1.1–2.0)
2 or more affected	29,105	13	44.7	1.1 (0.6–1.9)
Unknown	135,571	74	54.6	1.2 (0.9–1.6)
Grandmother				
No history	563,301	272	48.3	1.0 (reference)
Any affected	31,651	19	60.0	1.4 (0.9–2.2)
1 affected	29,988	18	60.0	1.4 (0.8–2.2)
2 or more affected	1663	1	60.1	1.3 (0.2–9.4)
Unknown	120,962	71	58.7	1.0 (0.9–1.5)
Aunt				
No history	476,814	228	47.8	1.0 (reference)
Any affected	102,142	57	55.8	1.3 (0.9–1.7)
1 affected	82,144	48	58.4	1.3 (1.0–1.8)
2 or more affected	19,998	9	45.0	1.0 (0.5–1.9)
Unknown	97,776	53	54.2	1.1 (0.8–1.5)

CI, confidence interval.

\* Adjusted for number of relatives, attained age, and breast cancer diagnosis. The second-degree variables were also adjusted for a first-degree family history. Women who did not have relatives with breast cancer in that category formed the reference group for each group. Women with no sisters were excluded from analyses of risk associated with having a sister with breast cancer, women with no daughters were excluded from analyses of risk associated with having a daughter with breast cancer, and women with no aunts were excluded from analyses of risk associated with having an aunt with breast cancer.

**TABLE 3**  
Rate Ratios (RRs) for Ovarian Cancer Associated With a Family History of Breast Cancer by Age at Ovarian Cancer Diagnosis

	Age at ovarian cancer diagnosis*					
	<60 Years			≥60 Years		
	Person-years	No. of cases	RR (95% CI)	Person-years	No. of cases	RR (95% CI)
1 <sup>st</sup> -degree family history						
No history	248,347	82	1.0 (reference)	325,041	197	1.0 (reference)
Any affected	46,679	22	1.4 (0.9–2.2)	71,761	52	1.1 (0.8–1.4)
1 affected	42,214	15	1.1 (0.6–1.8)	67,037	40	1.0 (0.7–1.4)
2 or more affected	4466	7	4.2 (1.9–9.2)	14,724	12	1.3 (0.7–2.4)
Unknown	4831	1	0.5 (0.1–3.8)	9255	8	1.4 (0.7–2.8)
2 <sup>nd</sup> -degree family history						
No history	207,435	63	1.0 (reference)	247,591	151	1.0 (reference)
Any affected	57,654	26	1.5 (1.0–2.4)	67,663	48	1.3 (0.9–1.8)
1 affected	44,251	24	1.8 (1.1–3.0)	51,961	37	1.3 (0.9–1.9)
2 or more affected	13,403	2	0.5 (0.1–2.0)	15,702	11	1.4 (0.7–2.5)
Unknown	34,769	16	1.6 (0.9–2.9)	100,803	58	1.1 (0.8–1.5)

CI, confidence interval.

\* RRs adjusted for number of relatives, attained age, and personal breast cancer diagnosis. The second-degree family history variables were also adjusted for a first-degree family history. Women who did not have relatives with breast cancer in that category formed the reference group for each comparison group.

**TABLE 4**  
Rate Ratios (RRs) of Ovarian Cancer Associated with Family History of Breast Cancer among Women With a Personal History of Breast Cancer

Relative	No. of person-years	No. of cases	Adjusted* RR (95% CI)
Any family history			
No history	30,811	24	1.0 (reference)
Any affected	27,269	25	1.3 (0.7–2.4)
1 affected	17,730	12	1.0 (0.5–2.0)
2 or more affected	9539	13	1.9 (1.0–3.9)
Unknown	10,241	6	0.8 (0.3–2.1)
Any 1 <sup>st</sup> -degree			
No history	48,420	34	1.0 (reference)
Any affected	18,270	21	1.7 (1.0–2.9)
1 affected	14,556	11	1.2 (0.6–2.3)
2 or more affected	3714	10	3.7 (1.8–7.7)
Unknown	1631	0	—
Any 2 <sup>nd</sup> -degree			
No history	40,095	32	1.0 (reference)
Any affected	14,215	10	0.9 (0.4–2.0)
1 affected	10,556	7	0.9 (0.4–2.1)
2 or more affected	3659	3	1.0 (0.3–3.5)
Unknown	14,010	13	1.4 (0.7–3.0)

CI, confidence interval.

\* Adjusted for number of relatives and attained age. The second-degree variables were also adjusted for a first-degree family history. Women who did not have relatives with breast cancer in that category formed the reference group for each group.

diagnosed at 60 years of age or older was not significantly elevated in women with a family history of breast cancer.

Among women with a personal history of breast cancer, the RRs increased with increasing number of affected relatives with breast cancer (RR = 1.9; 95% CI: 1.0–3.9 for 2 or more affected relatives), with that elevated risk due to having 2 or more affected first-degree relatives (RR = 3.7; 95% CI: 1.8–7.7) (Table 4). When further examined according to study subjects' age at breast cancer diagnosis, the increased risk associated with having 2 or more affected first-degree relatives was limited to women diagnosed with breast cancer before age 60 years (RR = 6.1; 95% CI: 2.5–15.0) (data not shown in table). The number of affected second-degree relatives was not associated with ovarian cancer risk overall, but risk was significantly increased in women diagnosed with breast cancer at age 60 or older (RR = 4.6; 95% CI: 1.2–17.5).

We further examined ovarian cancer risk according to extent of family history of breast cancer and age at breast cancer diagnosis and disease laterality among first-degree relatives with breast cancer (Table 5). Compared with women without a first-degree family history, women with 2 or more affected relatives, at least 1 of whom was diagnosed either before age 50 or with bilateral breast cancer, were at higher risk than women whose relatives were diagnosed at older ages or with unilateral breast cancer. RRs were highest among women with a personal history of breast cancer and 2 or more first-degree relatives with breast cancer, at

Risk of ovarian cancer before 60 years of age was significantly elevated among women with 2 or more affected first-degree relatives (RR = 4.2; 95% CI: 1.9–9.2) or 1 affected second-degree relative (RR = 1.8; 95% CI: 1.1–3.0) (Table 3). Risk of ovarian cancer

**TABLE 5**  
Rate Ratios (RRs) for Ovarian Cancer by Age of Diagnosis and Disease Laterality of First-Degree Relatives With Breast Cancer

		1 <sup>st</sup> -degree relative with breast cancer					
		Age at diagnosis*			Laterality status		
		<50	≥50	Unknown	Unilateral	Bilateral	Unknown
Any affected 1 <sup>st</sup> -degree relative <sup>†</sup>							
CA/PY	279/573,387	20/32,762	24/64,063	30/31,162	20/60,124	8/12,154	46/57,003
Rate <sup>‡</sup>	48.7	61.0	37.5	96.3	33.3	65.8	81.0
RR	1.0 <sup>§</sup>	1.4	0.8	1.5	0.7	1.5	1.4
95% CI		(0.9–2.2)	(0.5–1.2)	(1.0–2.2)	(0.5–1.1)	(0.7–2.9)	(1.0–1.9)
≥2 affected 1 <sup>st</sup> -degree relatives <sup>†</sup>							
CA/PY	343/696,724	11/8072	6/7670	2/3350	5/6026	5/2136	9/11,020
Rate <sup>‡</sup>	49.2	136.7	78.3	59.7	83.0	234.1	816.7
RR	1.0 <sup>§</sup>	2.6	1.3	0.9	1.4	4.2	1.4
95% CI		(1.4–4.8)	(0.6–3.1)	(0.2–3.5)	(0.6–3.5)	(1.7–10)	(0.7–2.7)
Personal history of breast cancer and any affected 1 <sup>st</sup> -degree relative <sup>†</sup>							
CA/PY	307/647,593	10/4484	4/9387	7/4303	6/8206	3/1870	12/8253
Rate <sup>‡</sup>	47.4	223.0	42.6	162.7	73.1	160.4	139.8
RR	1.0 <sup>§</sup>	3.5	0.7	1.8	1.2	2.6	1.7
95%/CI		(1.7–7.4)	(0.3–2.0)	(0.8–4.2)	(0.5–2.9)	(0.8–8.7)	(0.9–3.5)
Personal history of breast cancer and ≥2 affected 1 <sup>st</sup> -degree relatives <sup>†</sup>		<50	≥50	Unknown	Unilateral	Bilateral	Unknown
CA/PY	353/712,200	7/1574	3/1559	—	3/1131	3/476	4/2104
Rate <sup>‡</sup>	49.6	444.7	192.4	—	265.2	630.2	190.1
RR	1.0 <sup>§</sup>	6.5	2.8	—	3.6	8.3	2.4
95% CI		(2.7–16)	(0.8–9.4)	—	(1.1–12)	(2.4–28)	(0.9–7.0)

CI, confidence interval; CA, number of cases; PY, total person-years.

\* Age at diagnosis is the age of youngest relative in that category with breast cancer. All analyses are adjusted for attained age, number of first-degree relatives, and personal breast cancer diagnosis (the analyses among women with a personal history of breast cancer did not include this variable).

† At least one of whom had the age at diagnosis or laterality characteristic.

‡ Rate per 100,000 person-years of observation.

§ Women who did not have first-degree relatives with breast cancer form the reference category. If women with a personal history of breast cancer formed a group, the reference category also included women with this characteristic.

least 1 of whom was diagnosed before age 50 (RR = 6.5; 95% CI: 2.7–16.0) or with bilateral breast cancer (RR = 8.3; 95% CI: 2.4–28.0).

A family history of ovarian cancer was associated with an RR of 2.9 (95% CI: 1.7–4.9) after adjustment for a family history of breast cancer. Additional adjustment of RRs associated with a family history of breast cancer for family history of ovarian cancer in the subset of women who responded to the Phase IV questionnaire did not alter the RR estimates (data not shown).

## DISCUSSION

In this prospective study of 49,975 women, a family history of breast cancer was associated with an increased risk of ovarian cancer, particularly among women with 2 or more affected first-degree relatives.

Risk was even higher in this same subset of women if they were diagnosed with ovarian cancer before age 60, had a personal history of breast cancer diagnosed before age 60, or if at least 1 of their relatives had bilateral breast cancer or was under age 50 at breast cancer diagnosis. Women with a history of breast cancer in a second-degree relative were also at higher risk, but there was no dose-response with number of affected relatives.

The current study is consistent with most prior studies in showing some increased risk of ovarian cancer associated with a family history of breast cancer.<sup>3–11</sup> The results of prior studies according to features of family history characteristic of hereditary cancer syndromes have been inconsistent. Several studies reported no variation in ovarian cancer incidence<sup>7,10</sup> or mortality<sup>6,11</sup> with the number of first-degree relatives with breast cancer,<sup>10</sup> age at diagnosis

of proband<sup>7,11</sup> or relative,<sup>11</sup> or degree of familial risk, as estimated by a combination of the number of affected relatives and relatives' age at diagnosis.<sup>6</sup> Two of these studies were very small.<sup>10,11</sup> Two other studies reported variation in risk according to either assessed degree of familial risk based on a score derived from a kinship coefficient,<sup>4</sup> or the number of affected first-degree relatives and relatives' age at diagnosis among younger women.<sup>3</sup> Our study expands this literature substantially by prospectively assessing in older women the combined roles of first- and second-degree relatives, age at diagnosis in probands and relatives, laterality of breast cancer, and personal history of breast cancer. Although our results are based on small numbers of cases in certain cells, many of the RRs are statistically significant and the patterns of association are what one would expect for hereditary cancer syndromes.

The putative prototypic clinical features of hereditary cancer syndromes<sup>14</sup> have been derived almost exclusively from *descriptive studies* of high-risk families. The observed *quantitative associations* with regard to these features in our study—whose participants were not selected on the basis of family history of cancer—provide statistical confirmation of this clinical model. Furthermore, this familial risk, which is most likely genetic, is sufficiently strong to be detected in a general population setting.

The NIH Consensus Development Panel on Ovarian Cancer and the U.S. Preventive Services Task Force recommendations on genetic risk assessment and *BRCA* mutation testing noted the value of a comprehensive cancer family history taken by a knowledgeable physician and the value of special counseling for those at particularly high risk based on their family history.<sup>21,22</sup> Determining whether a positive family history is suggestive of a genetic predisposition requires knowledge of the site of cancer origin and ages at diagnosis in all close relatives.<sup>14</sup> Recent studies have documented that neither primary care providers<sup>23</sup> nor oncologists<sup>24</sup> routinely collect sufficient information on family history to permit making this assessment. The US Centers for Disease Control and Prevention has launched the Family History for Preventive Medicine and Public Health Initiative (<http://www.cdc.gov/genomics/activities/famhx.htm>) in an effort to correct this deficiency. Ironically, many women at high risk of ovarian cancer based on their family history of breast/ovarian cancer are interested in genetic testing, but are not receiving pertinent information or referrals with regard to their risk of ovarian cancer.<sup>25</sup>

Several methodological issues need to be considered in interpreting our results. We did not verify participants' reports of breast cancer in their relatives, but

previous studies have shown patient-reported family history of breast cancer in first-degree relatives to be accurate and valid for cancer risk assessment.<sup>15</sup> Reporting of family history of breast cancer in a second-degree relative is also reasonably accurate for breast cancer.<sup>15</sup>

We did not have complete information on family history of ovarian cancer, an established ovarian cancer risk factor.<sup>26</sup> Adjustment for this variable, however, did not alter the RRs in the subset of women who provided this information. Although patient-reported family history of ovarian cancer is considerably less accurate than that for breast cancer,<sup>15</sup> this information is important because the presence of both breast and ovarian cancer in a family significantly increases the likelihood that a *BRCA1/2* mutation will be detected.<sup>16</sup>

Finally, environmental risk factors clearly contribute to cancer risk as well.<sup>27</sup> Multiple persons with cancer in a family could reflect common lifestyle or other exogenous risk factors as well as genetic factors. However, we did not collect information on environmental risk factors from relatives of the participants, and thus we could not evaluate the contribution of shared nongenetic factors.

In summary, our data suggest that a more detailed family history of breast cancer—a low-tech but powerful tool—combined with an individual's age and personal history of breast cancer can be useful for identifying women at elevated ovarian cancer risk. Knowledge of the familial component of ovarian cancer risk can be used to inform decisions regarding whether to obtain genetic testing, screening, or undertake preventive measures.<sup>22</sup> In light of ovarian cancer's tendency to present at a late stage and its attendant high mortality rate, the need to identify women at particularly high risk is clear.

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